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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,395	11/20/2000	Stephen W. Fesik	6752.US.01	8628
23492	7590	06/17/2005	EXAMINER	
ROBERT DEBERARDINE ABBOTT LABORATORIES 100 ABBOTT PARK ROAD DEPT. 377/AP6A ABBOTT PARK, IL 60064-6008			HARRIS, ALANA M	
			ART UNIT	PAPER NUMBER
			1642	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/716,395

Applicant(s)

FESIK ET AL.

Examiner

Alana M. Harris, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 March 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 10-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 14 is/are allowed.
- 6) ☒ Claim(s) 1-8 and 10-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 18, 2005 has been entered.

2. Claims 1-8 and 10-14 are pending.

Claim 1 has been amended.

Claim 9 has been cancelled.

Claims 1-8 and 10-14 are examined on the merits.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 1, 2, 4-8 and 10-13 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

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the application was filed, had possession of the claimed invention is maintained. Claim 9 has been cancelled.

"Applicants' arguments in the previous Response [submitted April 30, 2004] are incorporated herein", see instant Remarks submitted March 18, 2005, page 4. Applicants support their arguments with statements from the USPTO Written Description Guidelines, as well as reiterate "the specification discloses not only the size range and make-up of the replacement sequence ... derived from a wild-type human Bcl-2 protein..."., see page 5 of Remarks. Applicants direct the Examiner's attention to the bridging sentence of pages 7 and 8 and page 7, lines 15-20. Applicants conclude arguments asserting they were in possession of the claimed genus. These arguments and points of view have been fully considered, but found unpersuasive.

The Examiner has reviewed all of the sections of the specifications pointed out by the Applicants and it remains clear that Applicants have not sufficiently described an adequate number of members of the claimed genus. Applicants clearly have one species of the claimed genus, a mutant Bcl-2 protein consisting of 166 amino acid residues identified as SEQ ID NO: 2 comprising the replacement sequence consisting of 16 amino acid residues identified as SEQ ID NO: 1. However, Applicants assert claim to innumerable mutant Bcl-2 proteins that *can* contain 150 to 180 amino acid residues, wherein the replacement sequence is not limited by the type or number of acidic amino acids comprising said sequence. Likewise, there is not adequate description of the flexible loop, which the replacement amino acid is to replace an undefined portion of said loop. The specification does not adequately describe structure of these mutant

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proteins coupled with function. The mutant proteins claimed do not provide define the nexus that must exist between the structure of the protein and the function.

Furthermore, there is no description of the amino acids residues on the amino terminus and carboxy terminus surrounding the replacement sequences. While the claims provide that the mutant protein must be *derived* from a wild-type human Bcl-2 protein. The art establishes three isoforms of wild-type bcl-2, with particularity two of the three isoforms have two different sizes, bcl-2 α consisting of 239 amino acid residues and bcl-2 β consisting of 205 amino acid residues, see Reference C1 from IDS submitted March 19, 2003; Reference C5 from IDS submitted March 26, 2003; instant specification, page 4, lines 7-11 and page 6, lines 17-30 and Figure 1. Applicants have not pointed expressed which "wild-type bcl-2" protein the mutant protein should arise from.

As noted in the Final Office Action mailed July 27, 2004 "[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice...", see 1242 OG 174, column 1, section 2, January 30, 2001. The claims continue to set forth a genus, which includes mutant proteins with substantial variation. "For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.", see 1242 OG 174, column 1, section 2, January 30, 2001. For the reasons of record and set forth above the rejection is maintained.

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5. The rejection of claims 1, 2, 4-8 and 10-13 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained. Claim 9 has been cancelled.

Applicants state "[their] arguments in the previous Amendment are incorporated herein.", page 6 of Remarks. Applicants assert "the specification provides detailed information regarding the replacement of the amino acids in the flexible loop...", see page 6, paragraph 3 of Remarks. Applicants also state methods of preparing these mutant proteins are described in the specification and there are screening assays to identify candidate compounds capable of binding to the claimed mutant proteins. Applicants conclude with arguments directed to 35 USC § 101 rejections, which are not of record in the Final Office Action or the instant action and note they have a manageable pool of mutant proteins. These arguments and points of view have been carefully considered and have been found unpersuasive.

It is believed Applicants are referencing the 35 USC § 112, enablement rejection when they cite 35 USC § 101. This statute and conditions thereof are moot. A manageable pool is regarded as a set of members with well defined limitations opposed to a set of members within a vast pool not limited by amino acid length, amino acid residues or function. Applicants claimed mutant proteins have arbitrary parameters governing said proteins. For instance, mutant Bcl-2 proteins that *can* contain 150 to 180 amino acid residues, wherein the replacement sequence is not limited by the type

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or number of acidic amino acids comprising said sequence. These limitations or lack thereof do not provide for easily assessing the set one of ordinary skill in the art should work from. The screening assays Applicants note in their Remarks are not to definitively identify the plethora of mutant proteins, but candidate compounds, which are capable of binding to the mutant proteins. These assays do not aid in identifying Applicants claimed invention. Without guidance as to how to "zero in" and differentiate between all of these mutant proteins, make these proteins and use these proteins the broadly claimed invention is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

6. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained and newly made. Claim 9 has been cancelled.

Applicants assert in an effort to expedite prosecution of the instant application they have amended claim 1 to include the exact amino acid position of the flexible loop, see Remarks submitted March 18, 2005, bridging paragraph of pages 7 and 8. This assertion has been carefully considered, but found unpersuasive.

a. The recitation "flexible loop" in claims 1 and 2 is vague and indefinite. As noted in the Final Action mailed July 27, 2004, page 5, section a. it follows that the loop is essential to the wild-type and mutant human Bcl-2 proteins, however it is not clear what defines the loop, i.e. amino acid residues, structural juxtaposition. Applicants have

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not adequately defined the flexible loop. Accordingly, the metes and bounds cannot be determined and the rejection is maintained.

b. Claim 1 is indefinite in the recitation "...wherein the amino acid residues which encode said flexible loop...". Amino acids do not encode proteins or polypeptides. The recitation is not proper and should be amended to reflect art known principles.

c. Claims 1 and 2 are vague and indefinite in the recitation "at least a portion of a flexible loop". It remains unclear how many amino acids coding for the flexible loop would be necessary to maintain structure and function. And while Applicants submit that the flexible loop of Bcl-x is not required for maintaining the integrity of the protein or retaining function this does not absolve the instant rejection. The term, flexible loop is still nebulous and lacks adequate description and characterization. Accordingly, the metes and bounds are unclear.

d. Claim 1 is indefinite in the recitation "...a wild-type human Bcl-2 protein...". It is not clear which isoform is being identified as the wild-type human Bcl-2 protein, therefore the recitation is not definitive. Likewise, the recitation "...amino acids 35-91 of said human Bcl-2 protein" is indefinite.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,214,986 (filing date June 2, 1999) is maintained.

Applicants argue the wild-type Bcl-2 protein is defined in the specification and any amino acid sequence comparison of the prior art should be with certain sequences opposed to others. Applicants also assert that due to the amendment of claim 1, patent '986 is not applicable as anticipatory art. These points of view and arguments have been carefully considered, but found unpersuasive.

As noted in the Final Action the claims are given the broadest interpretation. Applicants' claims read on a mutant protein derived from a wild-type Bcl-2 protein. As pointed out in the 112,2nd paragraph rejection, section d the recitation "wild-type human Bcl-2 protein" is not definitive. Moreover, in light of the terms, "mutant" and "derived"

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one of ordinary skill in the art clearly infers that there are changes and variations in the amino acid sequence. Applicants' independent claim is remiss of a sequence identifier and does not include details of the protein including the complete structure, amino and carboxy termini. Arguments directed to SEQ ID NO: 3-6 are not commensurate because the claims do not include these sequences.

Sequence 2 of patent '986 is representative of a human mutant protein containing a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1 as established in the databases sheets included with the FAOM. The disclosed mutant protein reads on Applicants' broadly claimed mutant protein possessing all the properties of that claimed. The instant rejection is maintained for the reasons of record and set forth in the FAOM.

9. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent number 5,646,008 (July 8, 1997) is maintained.

Applicants' arguments are essentially the same as presented above in the 102(e) rejection. These points of view have been carefully considered, but found unpersuasive.

As noted in the Final Action the claims are given the broadest interpretation. Applicants' claims read on a mutant protein derived from a wild-type Bcl-2 protein. As pointed out in the 112,2nd paragraph rejection, section d the recitation "wild-type human

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Bcl-2 protein" is not definitive. Moreover, in light of the terms, "mutant" and "derived" one of ordinary skill in the art clearly infers that there are changes and variations in the amino acid sequence. Applicants' independent claim is remiss of a sequence identifier and does not include details of the protein including the complete structure, amino and carboxy termini. Arguments directed to SEQ ID NO: 3-6 are not commensurate because the claims do not include these sequences. Accordingly, the rejection is maintained.

10. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by Boise et al. (Cell 74: 597-608, August 27, 1993/ IDS reference C3) is maintained.

Applicants' arguments are essentially the same as presented above in the 102(e) rejection. These points of view have been carefully considered, but found unpersuasive.

As noted in the Final Action the claims are given the broadest interpretation. Applicants' claims read on a mutant protein derived from a wild-type Bcl-2 protein. As pointed out in the 112,2nd paragraph rejection, section d the recitation "wild-type human Bcl-2 protein" is not definitive. Moreover, in light of the terms, "mutant" and "derived" one of ordinary skill in the art clearly infers that there are changes and variations in the amino acid sequence. Applicants' independent claim is remiss of a sequence identifier and does not include details of the protein including the complete structure, amino and carboxy termini. Arguments directed to SEQ ID NO: 3-6 are not commensurate

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because the claims do not include these sequences. The instant rejection is maintained for the reasons of record and set forth in the FAOM.

11. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by Muchmore et al. (Nature 381:335-341, May 23, 1996/ IDS reference C7 is maintained.

Applicants' arguments are essentially the same as presented above in the 102(e) rejection. These points of view have been carefully considered, but found unpersuasive.

As noted in the Final Action the claims are given the broadest interpretation. Applicants' claims read on a mutant protein derived from a wild-type Bcl-2 protein. As pointed out in the 112,2nd paragraph rejection, section d the recitation "wild-type human Bcl-2 protein" is not definitive. Moreover, in light of the terms, "mutant" and "derived" one of ordinary skill in the art clearly infers that there are changes and variations in the amino acid sequence. Applicants' independent claim is remiss of a sequence identifier and does not include details of the protein including the complete structure, amino and carboxy termini. Arguments directed to SEQ ID NO: 3-6 are not commensurate because the claims do not include these sequences. The instant rejection is maintained for the reasons of record and set forth in the FAOM.

12. Claim 14 is free of the art.

Allowable Subject Matter

13. Claim 14 is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner can normally works a flexible schedule, however she be reached between the hours of 6:30 am to 5:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Alana M. Harris, Ph.D.
09 June 2005

**ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER**